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Three dysconnectivity patterns in treatment-resistant schizophrenia patients and their unaffected siblings

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ABSTRACT

Among individuals diagnosed with schizophrenia, approximately 20%–33% are recognized as treatment-resistant schizophrenia (TRS) patients. These TRS patients suffer more severely from the disease but struggle to benefit from existing antipsychotic treatments. A few recent studies suggested that schizophrenia may be caused by impaired synaptic plasticity that manifests as functional dysconnectivity in the brain, however, few of those studies focused on the functional connectivity changes in the brains of TRS groups. In this study, we compared the whole brain connectivity variations in TRS patients, their unaffected siblings, and healthy controls. Connectivity network features between and within the 116 automated anatomical labeling (AAL) brain regions were calculated and compared using maps created with three contrasts: patient vs. control, patient vs. sibling, and sibling vs. control. To evaluate the predictive power of the selected features, we performed a multivariate classification approach. We also evaluated the influence of six important clinical measures (e.g. age, education level) on the connectivity features. This study identified abnormal significant connectivity changes of three patterns in TRS patients and their unaffected siblings: 1) 69 patient-specific connectivity (PCN); 2) 102 shared connectivity (SCN); and 3) 457 unshared connectivity (UCN). While the first two patterns were widely reported by previous non-TRS specific studies, we were among the first to report widespread significant connectivity differences between TRS patient groups and their healthy sibling groups. Observations of this study may provide new insights for the understanding of the neurophysiological mechanisms of TRS.

1. Introduction

Schizophrenia is one of the most chronically disabling psychiatric illnesses with a global median lifetime morbid risk of 7.2/1000 persons (McGrath et al., 2008). In addition, around 20%–33% of all schizophrenia patients are diagnosed as drug treatment resistant schizophrenia (TRS) (Essock et al., 1996). TRS patients usually suffer a more severe form of the disease with inadequate symptom control from existing treatment antipsychotic (Kane et al., 1988; Kerwin and Bolonna, 2005). The atypical antipsychotic drug, Clozapine, remains the most effective medicine for TRS patients (Kane and Correll, 2010). However, approximately 1/3 to 2/3 of TRS patients do not fully respond even to Clozapine treatment (Cipriani et al., 2009). Despite the recent advances in pharmacotherapy, TRS remains a major clinical challenge (Bilic et al., 2014).

Although etiology of schizophrenia remains unclear, recent studies hypothesized that schizophrenia may be associated with altered multi-dimensional brain connectivity (Kalkstein et al., 2010; Konrad and

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Table 1
Functional connectivity studies of schizophrenia patients and their healthy siblings through year 2009.

Studies	Patient/sibling/control	Study aims	Shared CNs	Patient-specific CNs	Compensatory CNs in healthy siblings
Whitfield-Gabrieli et al. (2009)	13/13/13 (Sibling age 22.0 ± 2.9)	To investigate brain functional connectivity in TNN	Reduced task-related suppression in medial prefrontal cortex (MPFC)	Reduced anticorrelation between medial prefrontal cortex and right dorsolateral prefrontal cortex	None
Woodward et al. (2009)	25/12/32 (Sibling age 36.9 ± 13.3)	To investigate CRT in SCZ patients and their healthy siblings	Overall connectivity between right dlPFC and multiple brain regions were reduced; changes were mild in unaffected sibling	None	None
Repovs et al. (2011)	40/31/15 + 18 siblings of healthy control subjects (Sibling age 24.3 ± 3.7)	To investigate brain functional connectivity in TNN and three cognitive control networks (frontal-parietal, cingulo-opercular, and cerebellar)	Reduced connections among brain networks critical to cognitive control	None	None
Liu et al. (2012)	25/25/25 (Sibling age 25.6 ± 6.8)	To investigate brain functional connectivity in TNN and TPN	Increased connectivity between the bilateral inferior temporal gyri.	Increased connectivity between: 1 Posterior cingulate cortex/precuneus and left inferior temporal gyrus; 2 Ventral medial prefrontal cortex and right lateral parietal 3 Left dorsolateral prefrontal cortex and right inferior frontal gyrus.	None
Meda et al. (2012)	70/70/118 (Sibling age 40.8 ± 15.6)	To investigate brain functional connectivity in 16 fMRI resting state networks.	None	Abnormal connectivity between: 1 Fronto/occipital and anterior default mode/ prefrontal 2 Meso/paralimbic, and sensory-motor.	Discussed as the limitations of the work
Yu et al. (2013)	24/25/22 (Sibling age 12.5 ± 2.5)	To investigate the heritable characters of SCZ using multiclass patterns	CNs within cerebellum and the prefrontal lobe, the middle temporal gyrus, the thalamus, and the middle temporal poles.	CNs within TNN, executive control network, and cerebellum.	Connectivity among: right precuneus, left middle temporal gyrus, left angular and left rectus; between left rectus and cingulate cortex

Note: CNs: connectivity features; TNN: task-negative network; TPN: task-positive network. SCZ: schizophrenia; dlPFC: dorsolateral prefrontal cortex; CRT: choice reaction time; fMRI: functional magnetic resonance imaging.

Winterer, 2008; Liang et al., 2006; Venkataraman et al., 2012), possibly caused by neural plasticity deficits in the brain (Daskalakis et al., 2008; Friston, 1998; Stephan et al., 2006). Many recent studies have used resting state functional magnetic resonance imaging (fMRI) to examine the functional dysregulations within and between different brain regions/networks in schizophrenia. Despite an abundance of such studies, results to date have been inconsistent (Bluhm et al., 2009; Camchong et al., 2011; Jafri et al., 2008; Ma et al., 2012; Mannell et al., 2010; Rotarska-Jagiela et al., 2010; Salvador et al., 2010; Venkataraman et al., 2012; Whitfield-Gabrieli et al., 2009; Yu et al., 2011; Zhou et al., 2007). Indeed, both increased and decreased connectivities have been observed in the default-mode, as well as other resting state networks (RSNs) in individuals with schizophrenia (Bluhm et al., 2009; Camchong et al., 2011; Jafri et al., 2008; Liang et al., 2006; Mannell et al., 2010; Rotarska-Jagiela et al., 2010; Salvador et al., 2010; Zhou et al., 2007).

In recent years, several studies have also compared changes in brain structure and function in patients with schizophrenia, their unaffected siblings and healthy controls. Some of these investigations focused on the anatomical study of certain brain regions (Gogtay et al., 2012; Hao et al., 2009; Harms et al., 2010), while others investigated the functional connectivity of specific brain networks (Gogtay et al., 2012; Guo et al., 2014; Guo et al., 2015; Liu et al., 2012; Meda et al., 2012; Repovs et al., 2011; Whitfield-Gabrieli et al., 2009; Woodward et al., 2009; Yu et al., 2011). Table 1 provides an overview of the functional connectivity studies conducted in the last 5 years. In an attempt to identify biological markers for schizophrenia, most of those studies looked at shared abnormalities between schizophrenia patients and their unaffected siblings, and consistently reported similar – though usually milder – alterations in individuals with schizophrenia and their unaffected siblings (MacDonald, III et al., 2009; Sitskoorn et al., 2004; Snitz et al., 2006; Toulopoulou et al., 2003). Their findings provided valuable information to elucidate the SCZ endophenotypes and led to a better understanding of the pathophysiology of schizophrenia.

However, few previous function connectivity studies focused on TRS patients let alone their unaffected siblings. In the present fMRI study, we studied and compared the whole brain connectivity features among TRS patients, their unaffected siblings, and a group of physically and psychiatrically healthy controls. We sought to create a global distribution map of the connectivity changes in both TRS patients and their unaffected siblings. To evaluate the influence of non-disease-symptom related factors on our connectivity study, we tested the correlation between six clinical measures and the connectivity features: 1) age; 2) education; 3) disease duration (DD); 4) onset age; and 5) duration of untreated psychosis (DUP), and 6) PANSS total score.

2. Materials and methods

2.1. Participants

Thirty-two individuals with schizophrenia participated in the study. Patients were recruited from the Kunming Mental Hospital and the First Affiliated Hospital of Kunming Medical College in Kunming, China. All 32 patients met *DSM-IV* diagnostic criteria for schizophrenia, as assessed using the *DSM-IV-TR* Structured Clinical Interview, Patient Version *(SCID-I/P)*. Patients had no history of neurological disorder, severe medical disorder, substance abuse, or electroconvulsive therapy.

All patients met criteria for TRS according to International Psychopharmacology Algorithm Project (IPAP, http://www.ipap.org/): (1) documented poor functioning for 5 years; (2) previous lack of response to therapeutic trials of at least two antipsychotic drugs from two different chemical classes; medications were administered for at least 4–6 weeks each at doses ≥ 400 mg equivalents (of chlorpromazine) or 5 mg/day (of risperidone); (3) moderate to severe psychopathology, especially positive symptoms, such as conceptual disorganization, suspiciousness, delusions, or hallucinatory behavior. And in practice, we use PANSS score to measure the symptom severity. All patients have a rating of at least moderate severity on one or more items on the positive symptom subscale of the Positive and Negative Syndrome Scale (PANSS), and having a total PANSS score ≥ 75. We would like to clarify that all 32 patients were receiving antipsychotic medications at the time of scanning (Clozapine [n = 10], Risperidone [n = 6], Olanzapine [n = 3], Clozapine + Risperidone [n = 3], Clozapine + Perphenazine [n = 4], or clozapine + quetiapine [n = 6]). It should be noted that TRS patients typically demonstrate a more severe form of the disease than non-TRS patients, and are less impacted by the drugs. Thus, we expected that connectivity variations in TRS patients would have more pronounced changes and thus are more detectable.

In addition, all but one of the TRS patients had an unaffected sibling. All 31 siblings exhibited no psychotic symptoms, either presently or in the past. The inclusion and exclusion criteria were the same as those used for the TRS patients, except that the siblings did not meet *DSM-IV* criteria for any Axis-I or Axis-II psychiatric disorder. Notably, most of the unaffected siblings had also passed the age at which schizophrenia typically manifests.

The control group comprised 44 physically and psychiatrically healthy controls from Kunming City and its surrounds. Inclusion and exclusion criteria were the same as for the sibling group, except that controls had no first-degree relative with a history of psychiatric disorders. Patients, siblings, and controls were well matched for sex, age, and education (see Table 2).

Risks and benefits of the study were presented in detail, and all participants gave written informed consent. If participants were not able to fill out the consent form, their guardians were contacted to fill out the consent form on the patients' behalf. The study was approved by the ethics committee of the Second Xiangya Hospital of Central South University, the ethics committee of the First Affiliated Hospital of Kunming Medical University (former name: the First Affiliated Hospital of kunming Medical College) and by the Institutional Review Board (IRB) of the National Institute of Mental Health (NIMH).

2.2. Imaging data acquisition

All brain scans were performed using a 1.5 T GE MRI scanner, with foam pads used to limit head motion and reduce scanner noise. Functional

Table 2
Demographic and clinical profiles of the schizophrenic patients, their unaffected siblings, and healthy controls.

Characteristics	Schizophrenic patients (n = 32)	Healthy siblings (n = 31)	Healthy controls (n = 44)
Age (year)	35.0 ± 37.99	35.74 ± 7.49	32.27 ± 7.45
Education (year)	8.91 ± 2.63	12.19 ± 3.33	8.82 ± 2.78
Sex (male/female)	15/17	10/21	16/28
Duration of illness (month)	151.61 ± 91.22		
PANSS scores			
Total	97.0 ± 8.7		
Positive symptoms	25.9 ± 2.6		
Negative symptoms	24.4 ± 5.2		
General psychopathology	46.4 ± 3.5		
Medication dosage (mg/day chlorpromazine equivalents)	445.3 ± 61.7		

scanning was carried out in darkness, with participants explicitly instructed to keep still, close their eyes, and relax during the scan. Functional images were acquired with gradient-echo echo-planar imaging with the following parameters: TR = 2.0 s, TE = 40 ms, field of view = 24 cm, acquisition matrix = 64 × 64, flip angle = 90°, in-plane resolution = 3.75 × 3.75 mm, slice thickness = 5 mm, gap = 1 mm, 24 slices, axial acquisition, and time points = 160.

2.3. Imaging data preprocessing

fMRI data were preprocessed using the Statistical Parametric Mapping (SPM5, http://www.fil.ion.ucl.ac.uk/spm/) and Resting-State fMRI Data Analysis Toolkit (REST, http://resting-fmri.sourceforge.net) software (Song et al., 2011). The first five time points from each functional run were discarded to allow for equilibration of the magnetic field. Remaining data were realigned using INRIalign, a motion-correction algorithm unbiased by local signal changes (Freire et al., 2002; Freire and Mangin, 2001). All participants included in this analysis had less than 1.5 mm maximum displacement in x, y, or z and less than 1.5° of angular rotation about each axis. In addition, we examined the peak displacements (Lowe et al., 1998) in each participant in three groups and found no significant difference (ANOVA, P-value > 0.05). Data were then spatially normalized into standard Montreal Neurological Institute (MNI) space (Friston et al., 1995), and the data (originally acquired at 3.75 × 3.75 × 6 mm^3) were slightly subsampled to 3 × 3 × 3 mm^3, resulting in 61 × 73 × 61 voxels. A linear regression process was used to reduce the effects of head motion and regress out constant elements and linear drift. All data were band-pass filtered (0.01–0.08 Hz) and were smoothed with a 3-dimensional (3D) Gaussian kernel of 6-mm full width at half maximum (FWHM) to reduce spatial noise. The WFU_PickAtlas toolbox (Maldjian et al., 2003; Maldjian et al., 2004) was used to generate the whole brain mask containing the 116 Anatomical Automatic Labeling (AAL) brain regions (Tzourio-Mazoyer et al., 2002) with 59,323 voxels.

2.4. Brain parcellation

For this study, whole brain was parcellated into 116 AAL brain regions used in several earlier studies of whole-brain connectivity (Konrad and Winterer, 2008; Liu et al., 2007; Salvador et al., 2010; Yu et al., 2013). With a voxel volume of 3 × 3 × 3 mm^3, this method divided the cerebra into 90 regions (45 per hemisphere) and the cerebella into 26 regions (nine in each cerebellar hemisphere, eight in the vermis); Supplementary Table 1 lists the 116 AAL brain regions.

2.5. Connectivity network feature map calculation

For each subject, connectivity network features (CNs) both within and between each pair of 116 AAL brain regions were calculated, generating a connectivity feature map (CFM) $\in R^{116\times116}$. We defined the CN between two brain regions Ω_1 and Ω_2 as the mean of the Pearson correlation coefficients calculated from each pair of voxels within the two regions, as given by Eq. (1):

$$CN = \begin{cases} \dfrac{\sum_{i,j\in\Omega_1, i\neq j} corr(v_i, v_j)}{n_1(n_1-1)} \\ \dfrac{\sum_{i\in\Omega_1, j\in\Omega_2} corr(v_i, v_j)}{n_1 n2} \end{cases} \quad (1)$$

where n_1 and n_2 are the total number of vectors within Ω_1 and Ω_2, respectively; $corr(v_i,v_j)$ is the Pearson correlation coefficients of two vectors after Fisher r-to-z transformation; and v_i and v_j are the time-course vectors for the ith and the jth voxels.

2.6. P-value map calculation and analysis

After CFMs were acquired for each of the 107 subjects, one-way ANOVA tests were conducted for each CN feature in three comparisons: patient vs. control, patient vs. sibling, and sibling vs. control, generating three P-value maps $\in R^{116\times116}$. The CNs showing significant differences in each contrast were selected and compared. The false discovery rate (FDR) (Benjamini and Yekutieli, 2005) procedure was used to control the expected proportion of false positives ($q = 0.01$). Brain regions associated with the selected CNs were then investigated, and results of the comparisons were presented in Venn diagrams.

2.7. Multivariate classification

Because statistical test P-values may not be the best measures of connectivity relevance (Venkataraman et al., 2012), we used a Euclidean distance-based multivariate classification method, followed by a leave-one-out (LOO) cross validation, to evaluate the predictive power of the selected CNs by ANOVA and further identify the most discriminative subsets of CNs for each contrast. The classifier is given by Eq. (2).

$$classID = \min_g \sum_{i=1}^{n_g} Eu(v_i, v_0)/n_g \quad (2)$$

where v_0 is the feature vector of a subject s_0 who is to be identified; *classID* is the label of the group to which subject s_0 belongs; v_i (i = 1,…,n_g) are the sample vectors in group g with n_g samples (not including s_0); and $Eu(*,*)$ is the Euclidean distance between two vectors of the same dimension. Here g = 1,2,3 for patient, control, and sibling groups, respectively.

The classifier inputs for this study included: 1) the selected CN values (sorted by ascending P-value) of the subject to be classified; and 2) the corresponding CN values of all other subjects in all three groups: patients, unaffected siblings, and controls. Biomarker sets of CNs that generated the highest classification ratio (CR) were chosen as having the most significance for the corresponding contrasts. When multiple sets of CNs exist corresponding to the highest CRs, we selected the least numbered features set.

2.8. Correlation between clinical measures and CNs

To evaluate the influence of clinical measures on the connectivity features, we calculated the Pearson correlation between each CN and each of six important clinical measures for TRS patients including: 1) age; 2) education; 3) disease duration; 4) onset age; 5) duration of untreated psychosis (DUP); and 6) PANSS total score. For healthy siblings and healthy controls, the influence of age and education was studied. For each clinical measure in each group, a clinical correlation map (CCM) was generated.

3. Results

First, 6786 CNs were analyzed via three comparisons: patient vs. control, patient vs. sibling, and sibling vs. control with one-way ANOVA. At the same significance level (P-value < $3.95e^{-4}$; corrected by FDR), we then selected and compared the top significant CNs for each contrast. Consequently, we used multivariate classification followed by LOO cross validation to test the effectiveness of the selected CNs, and studied the brain regions associated with the most effective CNs. Finally, we evaluated the influence of six important clinical measures on the CNs.

3.1. Significant CNs compared across three contrasts

The selected CNs can be categorized into three groups (see Fig. 1c which diagrams the amplitude distribution of the CNs in each category):

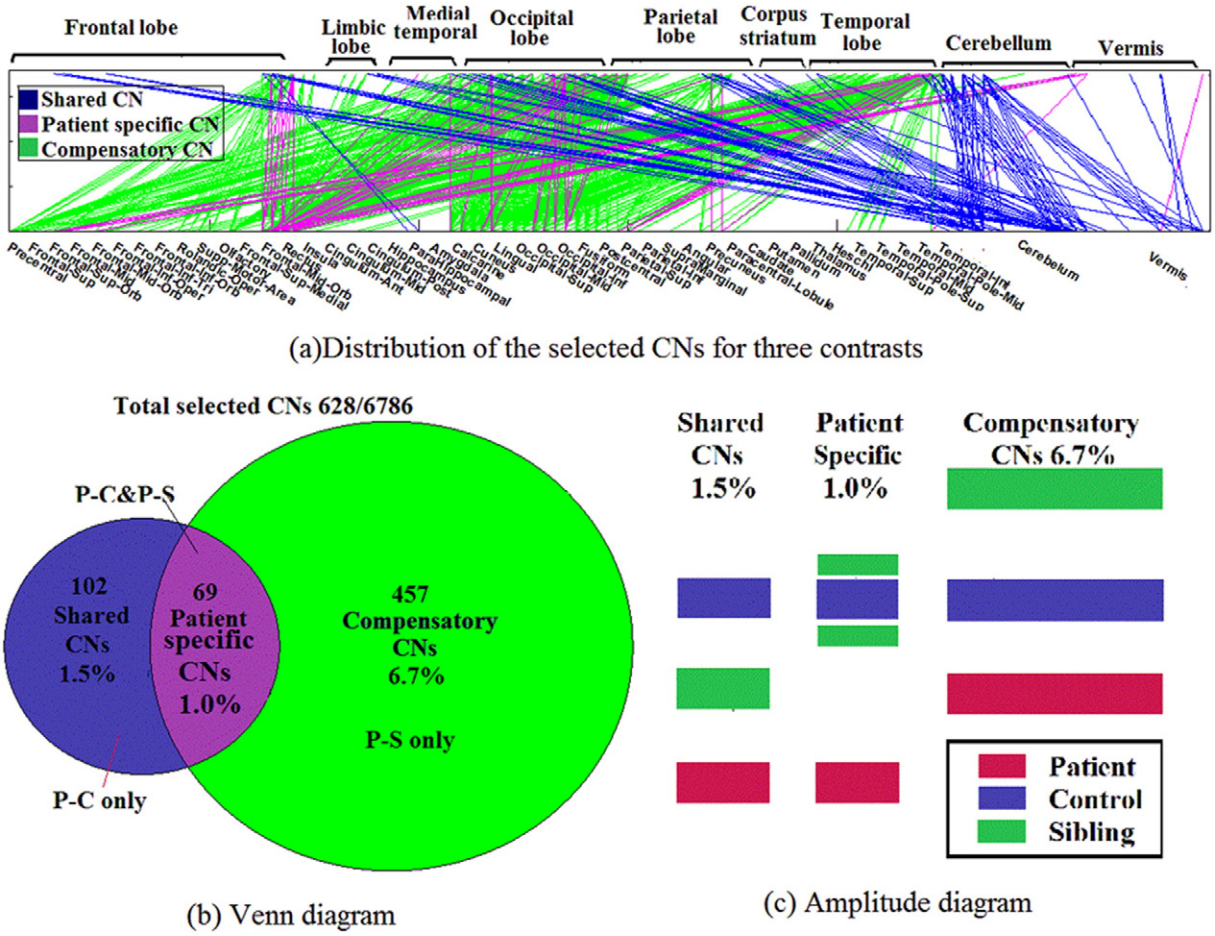

Fig. 1. Distribution of the selected connectivity features (including both intra- & inter- connectivities; P-value < $3.95E^{-4}$) for three contrasts: P–S, patient vs. sibling; P–C, patient vs. control; S–C, sibling vs. control. (a) The automatic distribution of the selected CNs; (b) the statistical distribution of the selected CNs; (c) amplitude distribution diagram of the selected CNs.

1) shared connectivity (SCN), where similar connectivity changes were present in both TRS patients and their unaffected siblings; these CNs were the ones only detected in the patient vs. control comparison. 2) Patient-specific connectivity (PCN), where only TRS patients showed significant changes but their unaffected siblings showed either subtle changes or no change compared to healthy controls; these CNs were detected in both the patient vs. control and patient vs. sibling comparisons; and 3) unshared connectivity (UCN), where the CNs differed significantly between patients and unaffected siblings but they were neither the SCN nor PCN, suggesting that they were absent in the patient/control comparison. Those CNs were detected only in the patient vs. sibling comparison. The automatic (Fig. 1a) and statistical (Fig. 1b) distribution of the selected CNs are given in Fig. 1. We also provided the statistical box plot of the connectivity amplitude and P-values for those selected CNs in Supplementary Figs. 1 and 2.

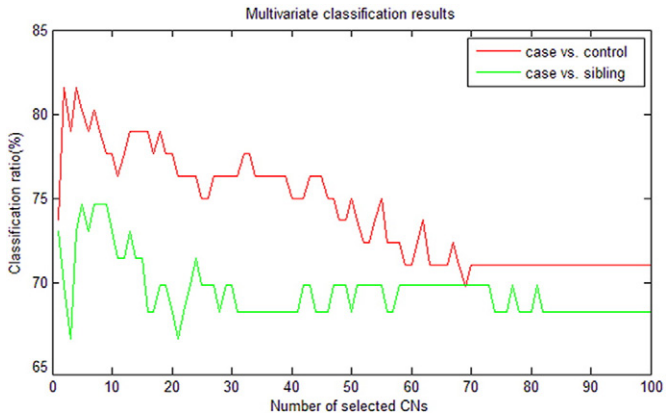

Fig. 2. Multivariate classification validates CN selection and identifies CN sub-sets with the most significance. The x-axis presents the number of features sorted in ascendant order by P-value from ANOVA. The y-axis presents the classification ratio (CR) using different numbers of CNs.

In this study, a total of $116 \times (116 + 1)/2 = 6786$ s were analyzed. At P-value < $3.95e^{-3}$ (corrected by FDR), approximately 1.5% (102/6786) of these CNs were identified as SCNs. As shown in Fig. 1a, those SCNs were mainly intra-cerebellum connectivity and connectivity between cerebellum and multiple cerebral cortexes including prefrontal lobe, occipital lobe, paracentral lobule, and thalamus. Approximately 1% (69/6786) CNs appeared to be PCNs, which were associated with cerebellum, default mode networks (e.g. rectus gyrus, parahippocampal gyrus, middle temporal gyrus) and part of the prefrontal cortex (e.g. medial orbital part of superior frontal gyrus, gyrus rectus) (Fig. 1a). At the same significance level, we identified 6.7% (457/6786) UCNs in unaffected siblings, where TRS patients showed moderate reduced connectivity compared to healthy controls while their unaffected siblings demonstrated increased connectivity (Fig. 1c). Noteworthy, those UCNs were widespread, especially between the occipital and frontal lobes, and between the parietal and temporal lobes (Fig. 1a). No significant CNs were identified in the sibling vs. control comparison.

The identified CNs from both the patient vs. control and patient vs. sibling comparisons were associated with large areas of the brain. Indeed, approximately 50% of all brain regions were associated with these selected CNs in the patient vs. control comparison — a percentage that rises to 59.5% (with an overlap of 31.9%) in the patient vs. sibling comparison.

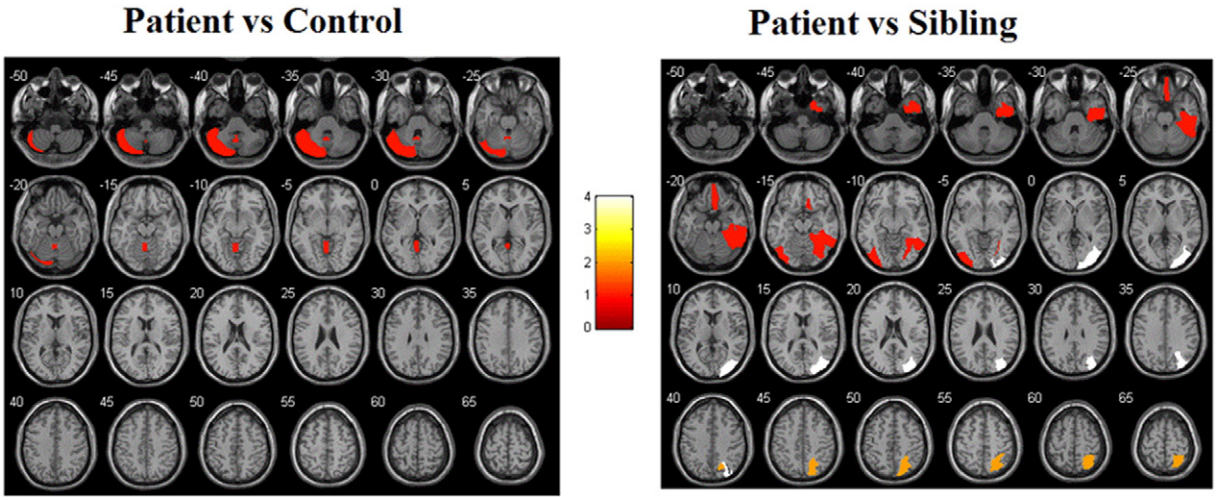

Fig. 3. Brain regions associated with most significant connectivity features comparing results from two studies in three different contrast groups (P−S = patient vs. healthy sibling; P−C = patient vs. control). Color coding represents number of significant connectivity features associated with each brain region.

3.2. Multivariate classification

To evaluate the predictive power of ANOVA-selected features and identify those CN subsets that were most discriminative, a multivariate classification analysis, followed by a LOO cross validation, was also conducted. Fig. 2 details the classification results differentiating each pair of groups for the patient vs. sibling and patient vs. control comparisons, respectively, using CNs selected from the corresponding contrasts (i.e. using CNs selected from the patient vs. sibling comparison to differentiate TRS patients from siblings, etc.). As shown in Fig. 2, the highest CRs were: patient vs. control = 81.6% with 2 CNs (CN between Vermis_9 and Vermis_4_5; between right Cerebelum_Crus2 and right Cerebelum_Crus1); patient vs. sibling = 74.6% with 5 CNs (CN within middle occipital gyrus; CN between middle occipital gyrus and both sides of the fusiform gyrus; CN between superior parietal lobule and left gyrus rectus and left inferior temporal gyrus).

The brain regions associated with the most discriminative CNs in the patient vs. sibling and patient vs. control comparisons are presented in Fig. 3.

3.3. Correlation between CNs and clinical measures

For each clinical measure in each group (patient, sibling, control and all subject in one group), a clinical correlation map (CCM) was generated by recording the Pearson correlation coefficients between the specific clinical measure and all the CNs in a specific group. Our study showed that clinical measures had weak yet different effect on the CNs derived from those groups, as shown in Table 3.

4. Discussion

This study compared global functional connectivity in the brains of TRS patients, their unaffected siblings, and un-related healthy controls. Three types of abnormal CNs detected were: SCNs, PCNs, and UCNs.

In the comparison between TRS patients and healthy controls, approximately 2.5% (171/6786) CNs were detected; these included both SCNs and PCNs (Fig. 1b). Those CNs were widespread within cerebra and between cerebellum and cerebra (58/116 AAL brain regions). Among those selected CNs, approximately 1% (69/6786) were PCNs. The PCNs involved the cerebellum, default mode network (e.g. rectus gyrus, parahippocampal gyrus, middle temporal gyrus) and prefrontal cortex (e.g. medial orbital part of superior frontal gyrus, gyrus rectus). Our observations support the hypothesis put forth in earlier non-TRS specific studies that schizophrenia is associated with widespread abnormal functional brain connectivity (Liang et al., 2006; Salvador et al., 2010; Venkataraman et al., 2012).

The findings in the present study also demonstrated that, among those 2.5% abnormal CNs detected in TRS patients, approximately 1.5% (102/6786) were shared by their unaffected siblings, albeit in milder

Table 3
Correlation between CNs and clinical measures in terms of CORR.

		Age	Education(year)	DD (month)	Onset age	DUP (year)	PANSS-TS
Patient	Range	[−0.16,0.33]	[−0.16,0.33]	[−0.16,0.33]	[−0.16,0.33]	[−0.16,0.33]	[−0.17,0.34]
	Mean ± std	0.11 ± 0.16	0.11 ± 0.16	0.11 ± 0.15	0.11 ± 0.16	0.11 ± 0.15	0.11 ± 0.15
	Abs < 0.2(%)	50.00%	50.01%	50.00%	50.02%	50.01%	50.13%
	Negative (%)	33.33%	33.33%	33.34%	33.33%	33.33%	33.35%
Sibling	Range	[−0.29,0.27]	[−0.33,0.32]				
	Mean ± std	0.07 ± 0.27	0.09 ± 0.32				
	Abs < 0.2(%)	98.31%	95.68%				
	Negative (%)	66.96%	59.88%				
Control	Range	[−0.22,0.30]	[−0.24,0.32]				
	Mean ± std	0.06 ± 0.30	0.07 ± 0.32				
	Abs < 0.2(%)	99.40%	98.14%				
	Negative (%)	35.01%	38.99%				
Combined three groups	Rang	[−0.00,0.15]	[−0.02,0.15]				
	Mean ± std	0.08 ± 0.05	0.08 ± 0.05				
	Abs < 0.2(%)	100.00%	100.00%				
	Negative (%)	0.04%	0.16%				

Note: 1. CORR: Pearson correlation coefficients; 2. DD: disease duration; 3. DUP: duration of untreated psychosis; 4. Abs: absolute value of the CORR.

form (Fig. 1b, c). Those CNs were mainly within the cerebellum and between the cerebellum and multiple cerebral cortices including the prefrontal lobe, occipital lobe, paracentral lobule, and thalamus. Prior non-TRS specific investigations had similarly found that unaffected siblings shared a milder version of the same connectivity changes as schizophrenia patients (Liu et al., 2012; Meda et al., 2012; Repovs et al., 2011; Woodward et al., 2009; Yu et al., 2013). However, our study did not detect any increase in shared CNs, which differed from some of the prior non-TRS specific studies (Liang et al., 2006; Liu et al., 2012). This may be due to subclinical features of the disorder (Venkataraman et al., 2012).

In addition to the SCNs and PCNs detected, we identified more UCNs in unaffected siblings (6.7% = 457/6786). Most of previous studies of general schizophrenia patients did not report UCNs as we observed in this study (see Table 1). For these UCNs, TRS patients showed moderately reduced connectivity compared to healthy controls while their unaffected siblings demonstrated increased connectivity (Fig. 1c). The UCNs were widespread, especially between the occipital and frontal lobes, and between the parietal and temporal lobes (Fig. 1a). A few of those connectivity changes occurred within the cerebellum or between the cerebellum and the cerebrum. These findings support the results from a recent whole brain connectivity study, although their study was not focused on TRS patients (45; see Table 1). We were one of the first to report widespread unshared functional connectivity changes in schizophrenia and the first one to report such observation in TRS specific groups.

It should be noted that no significant connectivity differences were found between unaffected siblings and healthy controls. Moreover, in unaffected siblings, many more UCNs than SCNs were detected. This observation was different from most of the previous observations which mainly detected SCNs (see Table 1) and was consistent with our experimental design in the following two ways. 1) All the SCZ patients were treatment resistant. TRS patients usually present more severe disease symptoms compared to healthy controls or healthy sibling; 2) all unaffected siblings recruited had no history of schizophrenia and, by the mean age of 35.74 ± 7.49, had exhibited no symptoms of the disease. Given that the age of onset for schizophrenia is typically 15–25 for males and 25–30 for females, it is likely that unaffected siblings would have developed compensatory mechanisms within their brains, which may lead to more functional difference from that of affected individuals. The younger age of the unaffected siblings in previous studies (see Table 1) may partially explain why few UCNs were identified.

Using the three types of abnormal CNs observed, we built a global anatomic distribution map of connectivity changes in both schizophrenia patients and their unaffected siblings (Fig. 1a). Fig. 1b presents the corresponding statistical distribution using a Venn diagram, and the connectivity amplitude distribution diagram is provided in Fig. 1c. Taken together, Fig. 1 helps illustrate the overall view of all identified functional connectivity changes related to TRS and their healthy sibling, including both SCNs and UCNs.

The multivariate classification method used to assess the predictive power of the selected CNs found that the highest CRs were 81.6% and 74.6% for TRS patient vs. control and patient vs. sibling comparisons, respectively (Fig. 3). Underscoring the validity of the selected variables, the accuracy of those predictions was comparable to or better than some recent 116 AAL brain region-based whole brain connectivity analyses; for instance, Venkataraman et al. (2012) obtained a prediction accuracy of 75%, and Yu et al. (2013) obtained a prediction accuracy of 62.0%. Interestingly, the strongest prediction accuracies were obtained using subsets that contained a small number of CN features: two CNs for patient/control identification (between Vermis_9 and Vermis_4_5; between right Cerebellum_Crus2 and right Cerebellum_Crus1), and five CNs for patient/sibling identification (CN within middle occipital gyrus; between middle occipital gyrus and both sides of the fusiform gyrus; between superior parietal lobule and left gyrus rectus and left inferior temporal gyrus). Notably, the identified brain regions associated with those CNs have all been previously implicated in non-TRS specific schizophrenia. Specifically, the gyrus rectus has been implicated in schizophrenia (Crespo-Facorro et al., 2000) and early depression (Ballmaier et al., 2004). The superior parietal lobule has been reported to show significant changes in schizophrenia patients (Yildiz et al., 2011). More recently, Fukuta et al.'s work showed that the gray matter in the left middle frontal gyrus presented significant change between postmenopausal patients and premenopausal patients (Fukuta et al., 2013). This consistency with earlier findings further confirms the validity of our results.

Although we speculated that the three patterns of different CNs detected in this study were due to the disease status of the three groups, these observations may be affected by other clinical factors such as age and education and medication history. To test and evaluate the potential influence of those clinical measures on the connectivity study performed, here we calculated the CCMs for each clinical measure in terms of Pearson correlation coefficients (CORR). As shown in Table 3, although the correlation of education in three groups was slightly different (0.16 ± 0.33, 0.09 ± 0.32, and 0.07 ± 0.32 for patients, healthy siblings and health controls, respectively), if tested as a whole group for all the subjects involved in this study, education (in year) had weak (100% CORR < 0.2) correlation with CN. This is consistent with previous studies that education level was not a significant moderator of correlations between schizophrenia neurological soft signs (NSS) and symptom severity or neurocognitive performance (Chan et al., 2010). Therefore, the higher education level in healthy siblings compared to patients and controls should not have significant influence on the CN analysis (see Table 2, the education year for patient, sibling and control groups are 8.91 ± 2.63, 12.19 ± 3.33 and 8.82 ± 2.78, respectively).

Boos et al. showed that the changes of fractional anisotropy (FA) of SCZ are different compared to healthy siblings and controls (Boos et al., 2013). In this study, the correlations between age and CNs were similar to that of between education and CNs. However, the age in three groups was well matched such that the influence of age on this connectivity study was even milder.

In addition to age and education, we also looked into the correlations between CNs and other four important clinical measures for the patient group: disease duration (DD, in month), onset age, duration of untreated psychosis (DUP, in year), and PANSS total score. Results showed that correlations between those parameters and CNs were similar to that of age and education, ranging among [−0.16, 0.33] with around 50% between [−0.2, 0.2]. This indicated that multiple factors worked together to affect the CNs for TRS patients, although each single factor contributed to a relatively small degree.

Among those clinical factors, DUP reflected the duration of medicine treatment. As similar to other factors that affect the CNs in TRS patients, DUP, or medication history, have limited influence on the CNs. Therefore, we had the reason to believe that the medicine history of TRS patients was not the main reason that caused the significant, widespread connectivity changes in the brain of TRS patients. Consequently, if we assume TRS patients and their healthy siblings sharing similarity in their brain connectivity, the widespread functional connectivity differences observed in this study were highly likely caused by the functional regulations in the brain of healthy siblings rather than the medicine-introduced changes in TRS patients. Since healthy siblings were not affected by medical treatment while sharing genomic burdens and partial environment conditions with TRS patients, the unshared connectivity changes compared to healthy controls observed in this group may reflect compensatory mechanism to protect against becoming ill.

It should be noted that AAL brain regions differ greatly in size. For large sized AAL brain regions, averaging the connectivity features for all the voxels within the region may cause mild level of information loss. Therefore, using finer grid for the brain parcellation may lead to better observation that is worthy of further study.

Despite the importance of these preliminary findings, this study also has several limitations. First, although we test the relation between connectivity features and duration of untreated psychosis (DUP), which reflects the medication history of the subjects and shows no significant correlation, we cannot absolutely secure that the medication exposure has no influence on our observations. Second, the sample size was small. To our knowledge, this is the first study to investigate functional whole brain connectivity changes in TRS patient group and their unaffected siblings. Although the predictive power of the selected CNs has been tested using a multivariate classification approach, it was not an extra validation step. The encouraging results suggest that further validation using larger datasets and a similar experimental design are warranted. Third, despite the fact that most of the unaffected siblings in this study had passed the age of peak first-onset risk for schizophrenia, a possible morbidity risk for the unaffected siblings remained. However, only 4 of 31 siblings were below the age of highest risk, which minimizes this possibility. Nevertheless, the unaffected siblings would still have a higher risk of developing schizophrenia in their later years than unrelated healthy controls. This minimal morbidity risk may still have influenced the reliability of the functional compensatory regulations detected. Forth, the education of siblings was higher than that of patient and control groups. Although the previous correlation studies and the current work suggested that education level does not have a significant influence on schizophrenia symptoms, matching the education level should further mitigate against this possibility. Fifth, although we speculate in this work that the significant CNs only detected in patient/sibling comparison may represent compensatory regulation, our findings were only partially consistent with another recent study (Yu et al., 2013), thus further studies are needed to confirm our findings. Finally, technical issues surrounding the data analysis methods used could have affected the results. Specifically, we used band pass filter of 0.01–0.08 Hz in data preprocessing and a Euclidean distance-based classifier to predict group differences. Other frequency bands and different classifiers may influence the results.

In conclusion, this study for the first time presented an abnormal connectivity change map in TRS patients and their unaffected siblings, revealed three types of dysconnectivities: patient specific, shared and unshared. This study is also one of the first to report widespread unshared significant functional connectivity in the unaffected siblings of TRS patients. With further validation using larger data sets, the results we obtained may provide valuable new insights into the understanding of neurophysiological mechanisms of TRS and its treatment.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2015.03.017.

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